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Vascular dementia neurovisual markers according routine and diffusion-tensor MRI (publications' review)

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The article presents review of the most significant neurovisual biomarkers-predictors of the cognitive disfunction caused by brain vascular pathology. Also given quantitative and qualitative characteristics of this pathology including localization that can be detected using routine and diffusion-tensor MRI. Following biomarkers were noted when using standard MRI protocols: atrophy of gray matter and white matter tracts and basal nuclei; white matter hyperintensities (foci of gliosis and periventricular leukoaraiosis), micro-bleeding (large vessels, white and gray matter deposits of hemosiderin), enlarged perivascular spaces (cystic enlargement of the penetrating arteries, arterioles, veins and venules), recent small subcortical infarcts and post-ischemic damages in cortex, basal nuclei and white matter tracts. The article outlines diffusion tensor MRI latest developments for cognitive deficits' risk assessment, such as threshold coefficients (indexes) of the fraction anisotropy, received in neocortex tracts (frontal and temporal lobes; fronto-thalamic pathway).

Keywords: diffusion-tensor MRI, fractional anisotropy, vascular dementia, cognitive disorders, brain atrophy, lacunar strokes, subcortical strokes, white matter hyperintensity.

Introduction

Increasing active life expectancy leads to the social significance of aging-associated diseases, such as senile dementia [1]. In the industrial countries, at the same time, considerable part of disorders, provoking dementia — besides neurodegenerative cerebral lesions — accounted for diseases of discirculatory character. This pathology is revealed not only for eldery patients, but also for a half of people aged from 50 to 65 years and for a quarter of population aged from 45 to 50 years. The main reason is chronic stress, which

plays one of the leading roles in pathogenesis of cardiovascular and cerebrovascular disorders, associated with vascular endothelium damage. Cognitive disorders may be identified for patients with arterial hypertension even in young and middle age at earlier stages of chronic cerebral ischemia [2; 3]. Thus, primary task of clinical medicine is to provide maximum possible early diagnostic of vascular brain damage, risk of initial cognitive deficit prediction for patients of young and middle age and prevention of dementia development, leading to disablement, for aged patients [4].

The importance of magnetic resonance tomography (MRI) for differential diagnosis of cerebral structures changes with certain damage patterns of cerebral cortex and pathways disease cannot be overestimated [5]. Even at initial stages of cerebral-vascular disease, when routine MRI is nonspecific, scarce and heterogenic — it is possible to determine micro-structural changes in cerebral tracts, responsible for cognitive function. Detection of white matter tracts damages, non-visible in case of routine MRI application, is possible unsing structural visualization technique — diffusion tensor MRI (DT-MRI) [6].

Current review contains the most prevalent and significant (for clinical medicine) neuroimaging markers, that could be detected using routine MRI and diffusion tensor MRI, and which could be predictors of cognitive dysfunction risk caused by cerebral vascular diseases.

Potential of the routine MRI

Using routine MRI, it is possible to obtain visual and quantitative estimate of morphologic changes, which may be used as bio-markers of cerebral vascular lesions. Advantage of the method is in its high diagnostic validity due to good contrast provided between different types of tissues [7].

Usually, diagnostics of the cognitive disorders caused by vascular diseases includes such specific markers as: diffusive atrophy of cortex (brain gray matter), atrophy of underlying structures (basal ganglion and deep pathways), white cerebral matter hyperintense (axons demyelination, transudative edema and gliosis), micro-haemorrhage (hemosiderin and amyloid deposition along cerebral vasculars), extension of perivascular spaces, presence of "fresh" infarctions and post-ischemic lacunar lesion in strategic cortex zones, basal nuclei and white fiber fascicles, responsible for cognitive function [8].

Hyperintensity of the white matter (HWM)

HWM is a neuroimaging term, describing cerebral white matter structure changes, visible at T2-weighted and FLAIR images as diffusive and local areas of hyperintensive (increased in respect of the rest vascular tissue) signal. These lesions are caused by the processes of axon demyelinization leading to their atrophy and in case of vascular pathology they appear in both brain hemispheres symmetrically. In 2013 the term "white matter hyper intensity" was proposed to be replaced the old names: "diffusive HWM" instead of "leukoaraiosis" and "local dotted or confluent HWM areas" instead of "foci of gliosis with dystrophic character". This decision was accepted in accordance with recommendations of International expert committee for development of small vessel disease visualization criteria and standards (STRIVE — Standards for ReportIng Vascular changes on Euroim-

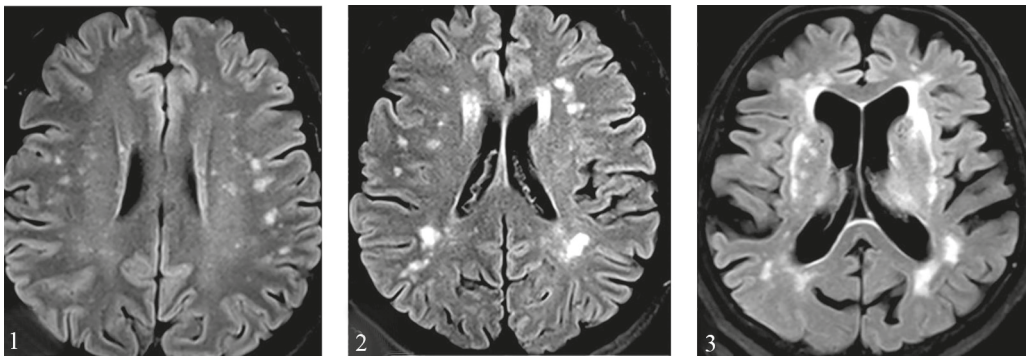

Fig. 1. Fazekas scale (Deep) for HWM estimation in deep subcortical zones. Axial sections in TIRM mode.

1 — single focus areas of HWM, 2 — presence of both single and partially confluent foci of HWM, 3 — confluent foci of HWM

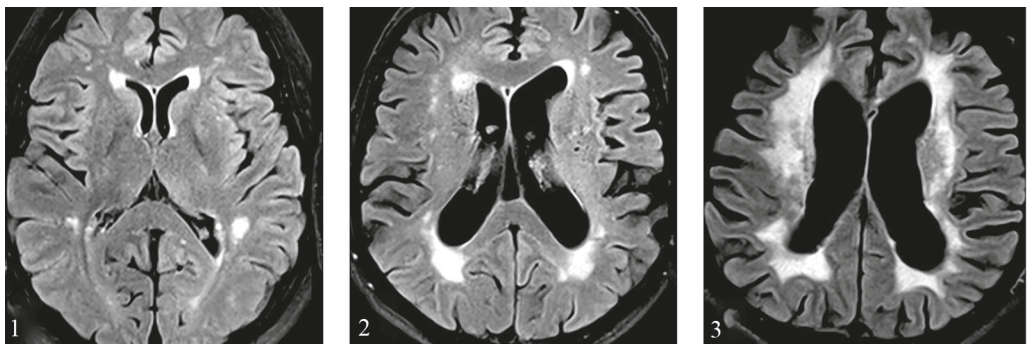

Fig. 2. Fazekas scale (PV) for HWM estimation around ventricles. Axial sections in TIRM mode.

1 — small HWM "caps" around ventricles' horns; 2 — moderate confluent zones of HWM; 3 — massive "confluent" zones of HWM

aging) [9]. It is recommended to differ periventricular HWM and deeply localized HWM (at advanced stages, the difference between these types of changes disappears), what is associated with blood circulation features [10]. In 1987, famous Austrian neurologist Franz Fazekas proposed to use qualitative scale for estimation HWM degree in different brain zones [11].

Fazekas scale (F) — visual scale for evaluation of periventricular HWM and HWM of deep localization. The scale is used for MRI in T2-weighted image mode (WI) with signal suppression from liquor — FLAIR or TIRM. HWM severity for deep localized white matter is estimated in the following way: F0 — HWM is absent; F1 — single foci of HWM, F2 — presence of both single and partially confluent foci of HWM, F3 — confluent foci of HWM (Fig. 1). For periventricular (PV) white matter: F0 — without HWM; F1 — small "caps" of HWM around ventricles' horns; F2 — moderate confluent perventricular zones of HWM; F3 — massive "confluent" zones of HWM, propagating from ventricles up to subcortical divisions (Fig. 2).

Evaluation of the cerebral white matter changes using Fazekas scale has an important prognostic value. According to Poggesi A., Gouw A. (2014) [12], HWM degree is

calculated as potential diagnostic indicator, correlated with cognitive disorder. Many authors associate double increase of dementia risk with augmenting of this trait [13; 14]. HWM is revealed upon hypertensive microangiopathy and cerebeal amyloid angiopathy, general clinical implications of which are repetitive strokes and progressive cognitive decline [15]. In case of hereditary microangiopathy (CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), where rough damage of white matter in anterior temporal, islet, external capsule and subcortical parts of the frontal lobes are main markers, HWM with diffuse charter manifest already in young age and correlates with early cognitive disorders [16]. Presence of pronounced HWM with lesion of deep subcortical regions is associated with apathy, depression and other psychiatric disorders, based on frontal disfunction. For patients with discirculatory encephalopathy, extensiveness of HWM lesison correlates with hyperpiesis severity and cognitive disorders [17].

Atrophy of the brain matter

Atrophy of brain matter (cerebral cortex and deep brain structures) is a neuroimaging indicator, accompanied by neurons loss and their axons as well, what makes it to be considered one of the pathological process markers, associated with cognitive disorders (Fig. 3). According to STRIVE, vascular pathology atrophic changes, characterized by progressing diffuse reduction of the head brain matter volume, are not associated with macroscopic local brain damages (such as trauma consequences or acute blood circulation disorder) and can be estimated by enlargement of external and internal liquor spaces comparatively to intracranial volume.

Cortical atrophy leads to subarachnoid cavities' and fissures increase, while volume of cerebral gyri decreases. Deep cerebral structures atrophy leads to increase of cerebrum lateral ventricles and the third ventricle. The latter causes frontal lobes function damage and its links with subcortical and stem divisions [18]. Internal hydrocephalus progression regarded as a more reliable criteria of cognitive disorders risk than visualization of focal subcortical HWM [19]. For rapid assessment of the atrophic lesions of deep cerebral tracts the following planimetric indications are sufficient: Index of lateral ventricle anterior horns and the width of the III ventricle (Fig. 4).

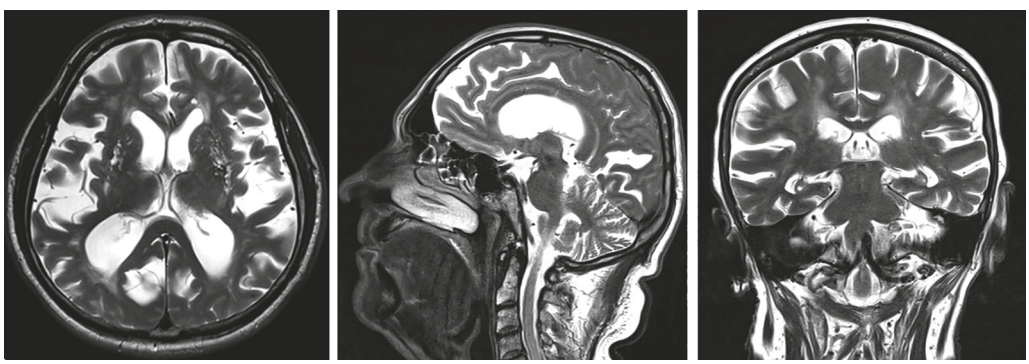

Fig. 3. Diffusive atrophy of cerebral matter

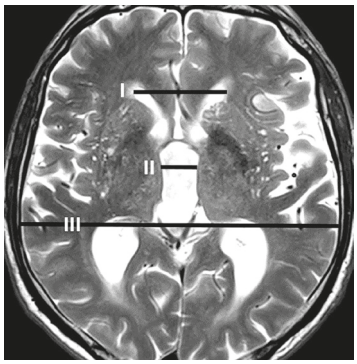

Fig. 4. Cerebral MR-image in axial projection obtained in T2-WI mode with determination of deep cerebral structures atrophy parameters. Line I — distance between lateral walls of lateral ventricle anterior horns. Line II — measurement of the third ventricle width. Line III — maximum distance between internal plates of calvarium bones

Anterior horns index (AHI) calculated by the formula I/III x 100 — where I is a distance between lateral walls of lateral ventricle anterior horns; III — maximum distance between internal bone plates of calvarium. Normal AHI indications for age group under 60 years are — 24.0–26.3, for group of 61 to 80 years — 28.2–29.4.

Width of the third ventricle is measured at the axial section by drawing the line, perpendicular to cerebral fissure in the middle of the third ventricle. Normal width of the third ventricle is the following: < 7 mm for adults aged under 60; < 9 mm for adults aged 60+ [20].

For estimation of the cortical atrophic brain changes and compensatory dilatation of the external subarachnoid cavities, visual scale of global (diffusive) cortical atrophy (GCA-scale) is applied, displaying changes from stage 1 to stage 4.

GCA-scale is a scale of the global cortical atrophy, which provides 13 cerebral zones estimation, generalizing brain changes in whole. Frontal, parieto-occipital and temporal sulci regions as well as ventricular system of each cerebral hemisphere were estimated separately using score from 0 to 3. Each of the anatomical structures mentioned above, estimated using the following scoring system: 0 — Normal volume / no ventricle expansion; 1 — sulci widening / moderate ventricle expansion; 2 — loss of sulci volume / considerable ventricles widening; 3 — "knife blade" type atrophy / expressed ventricle expansion (Fig. 5).

For now, the most accurate cortical atrophy estimation (especially for clinical observation in dynamics) requires MRI with application of specialized 3-D sequences and volumetric post-processing [21].

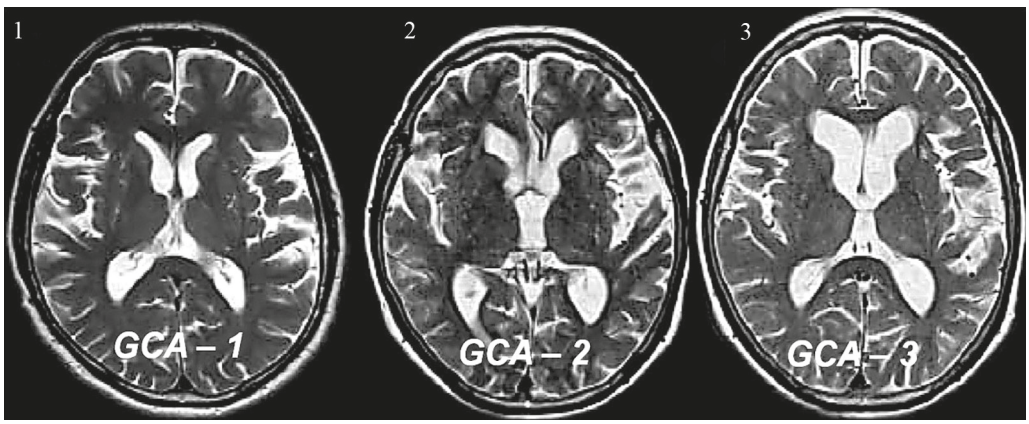

Fig. 5. Estimation of the cerebral atrophy severity using GCA-scale:

1 — sulci widening / moderate ventricle widening; 2 — loss of sulci volume / considerable ventricles widening; 3 — "knife blade" type atrophy / expressed ventricles widening

Cerebral microbleeds

Cerebral microbleeds (CMB) manifested by small (diameter is usually 2 to 5 mm, sometimes — up to 10 mm) rounded foci with low MR-signal intensity, which can be revealed using T2-weighted gradient recall echo images or other sequences, sensitive to magnetic fields heterogeneities, for example, SWI sequence (Susceptibility Weighted Imaging) (Fig. 6). Most often these changes are localized subcortically, in deep white and gray matter, brain stem and cerebellum and can be associated with amyloid deposition in vascular walls [22].

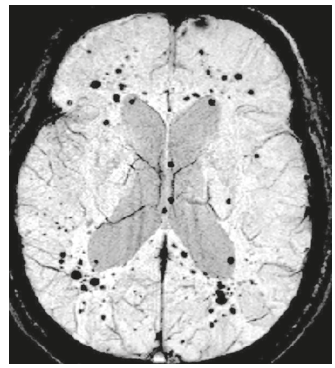

Fig. 6. Subcortical and periventricular cerebral microbleeds at axial section (multiple hyperintensive foci, visualized using SWI pulse sequence)

Cerebral microbleeds associated with aging and are typical for dementia progressing. For subjects with executive functions disorder this biomarker is detected predominately in frontal lobe and basal ganglia — areas, which are congenitally considered as neuroanatomical substrate for formation of cognitive, emotional and behavioral processes. According to some authors, cerebral microbleeds are not only predictors of "lobe type" cognitive disorders associated with executive disfunction, but also of memory disorders, speech dysfunction and visual-spatial orientation [23; 24].

Perivascular spaces (PVS)

PVS — spaces filled by liquid, located downstream penetrating arteries, arterioles, veins and venules, surrounded by leptomeningeal membrane [25]. This biomarker (Fig. 7), visualized using routine MRI, is an indicator of microangiopathy and associated with increasing risk of dementia development or cognitive function worsening [26]. Increasing perivascular spaces' size and their widening associated with HWM abundance and lacunar lesion can be considered as unfavorable prognostic sign [27].

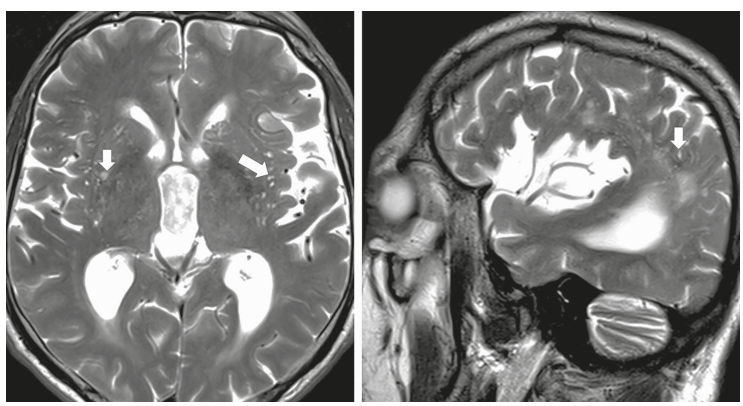

Fig. 7. Multiple widened perivascular spaces (bold arrows). Subcortical insular lobes (T2-WI, axial projection) and parietal lobe (T2-WI, sagittal projection)

Lacunar cysts (LC) and recent small subcortical infarction

Lacunar type of dyscirculatory changes with multiple postischemic cysts in zones, significant for cognitive functions, is unfavorable prognostic sign. Vascular genesis LC is a round or oval cavity with perifocal gliosis ferrule and liquor content, with diameter 3 to 15 mm (Fig. 8, 9A, 9B) [28; 29]. Perifocal gliosis around LC combined with no signs of MR-diffusion limitations signals that ischemic changes happen long time ago.

For designating "fresh" ischemia focus (with diameter < 20 mm) a term "recent small subcortical infraction" was proposed — infraction with clinical or neuroimaging data, confirming it was happened during last few weeks. To differentiate "fresh" and "old" focus (especially in respect of multi-foci cerebral lesion, when all foci conjugate between each other), DWI mode is preferable. DWI shows MR-diffusion signal amplification in the zone of blood circulation acute disorder at high (800, 1000) b-factor, while on ADC-map this signal is declining (Fig. 9B). After a while this area transforms into lacunar cyst or into large focus of gliosis, but there will not be any restrictions of MR-diffusion in this zone [30].

Sporadic asymptomatic lacunar infarctions may lead to secondary degeneration of adjacent white matter sectors, what leads to cortico-nuclear tracts disintegration, integra-

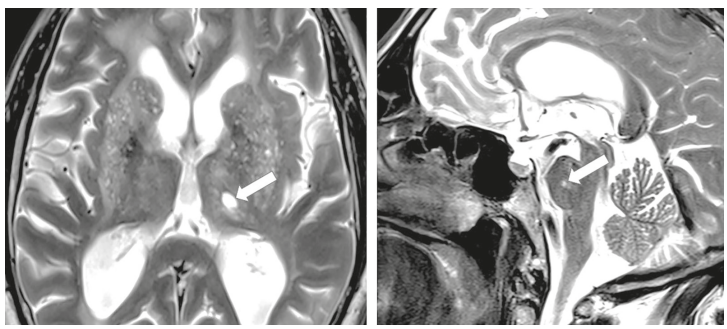

Fig. 8. Lacunar postishemic cyst, filled by liquor in the area of left thalamus (T2-weighted image, axial projection) and in the area of pons varolii (T2-weighted image, sagittal projection)

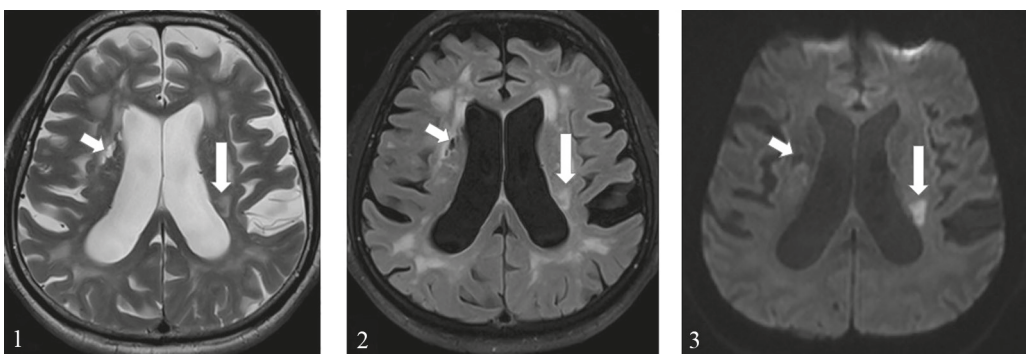

Fig. 9. Post-ishemic character lacunar cyst, basal nuclei, on right (small arrow), recent focal infraction in periventricular area on left (large arrow).

1 — T2-WI mode, 2 — TIRM mode, 3 — DWI mode. To differ «fresh» and «old» focus is possible only using DWI mode

tive cerebral activity and limbic system destruction because of associative fascicles interruption (among others — frontal thalamic pathway, ensuring bidirectional bond between nuclei of the thalamus, cingular gyrus and frontal cortex), decline of activating influence from the reticular formation and increase of cognitive disorders risk. Lacunar infarctions associated dementia manifested in such areas as: frontal lobes, parietal-temporal-occipital cerebral areas, mediobasal parts of temporal lobe, frontal and middle parts of thalami, pale globes, dentate nucleus of cerebellum hemisphere [31; 32].

Presence of any morphological anomaly increases patient's disability or death risks, however, few or moderate amount of macro-changes, received using routine MRI, can complicate prognosis of cognitive disorders of vascular genesis. The reason is that morphological substrates of chronic ischemic brain injury, resulting to cognitive deficit, are extremely non-specific. According to the data provided by some authors, standard MRI modes (T2-WI, T2FLAIR, SWI) can be applied only for white matter visual estimation, being not sufficient to measure severity of damage. To solve this problem, another MRI methods using pulse sequences, which are more sensitive to micro-structural damages, are required [33].

Potential of the diffusion tensor MRI

Diffusion tensor MRI shows micro-structural changes in axon myelin sheath and enables to estimate quantitatively severity of cerebral damages in a certain brain areas. The method provides application of pulse sequence in diffusion tensor imaging (DTI) with measuring dffusion in several directions and subsequent processing using post-processing programms, that provides opportunity to obtain certain numerical values of fractional anisotropy coefficient (CFA) and mean diffusion coefficient (MDC) in any region of interest [34].

The lower is CFA, the more the structure of cerebral tracts can be damaged. That's why DT-MRI is the most relevant method to detect the disease progression, demonstrating impressive potential for discirculatory damage severity differentiation [35]. Investigation of the pathophysiological mechanisms of cognitive dysfunction augmentation, steady correlation between severity of microstructural changes of main white matter tracts and clinical disorders was found. That fact proves advisability of DT-MRI use to detect disease already from subclinical lesion of cerebral structures stage [36].

Neocortical structures of fronto-temporal lobes are considered as strategically significant for cognitive activity [37]. Some authors highlighted three zones, responsible for cognitive function: Anterior Corona Radiata (ACR) (fig.10, zone 1), inferior longitudinal fascicle (ILF) (Fig. 10, zone 2) and Anterior Limb of the Internal Capsule (ALIC) (Fig. 10, zone 3). According to their data, investigating microstructural changes in these fascicles, it is possible to determine diagnostic ranges of vascular genesis' cognitive disorders development risk and to define CFA threshold absolute values [38], or their indices in respect to region of interest.

Indices of fractional anisotropy coefficient (CFA) as cognitive disorders markers. Using indices instead of absolute CFA values is more practical and less complicated method: the results not depend anymore of possible measurement difference, that can appear because of different magnetic field strength, or when equipment of different MRI producers is used; certain special methods to measure CFA manually are not required (that is con-

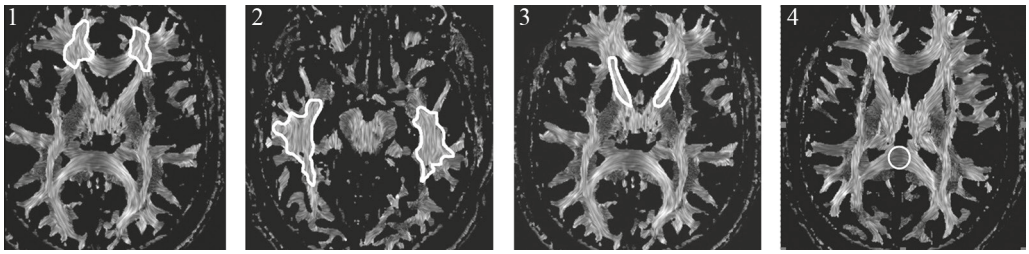

Fig. 10. Black and white map of factional anisotropy in axial projection.

1 — Anterior Corona Radiata (ACR), 2 — Inferior Longitudinalis Fasciculus (ILF), 3 — Anterior Limb of the Internal Capsule (ALIC), 4 — central parts of splenium of corpus callosum

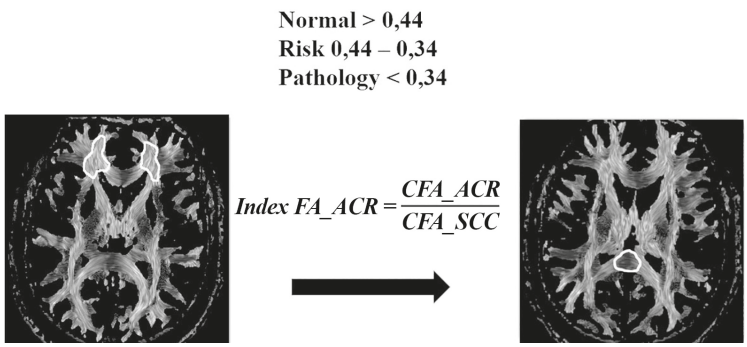

Fig. 11. Threshold values of CFA indices for Anterior Corona Radiata (ACR) as neuroimaging markers of cognitive impairment risk

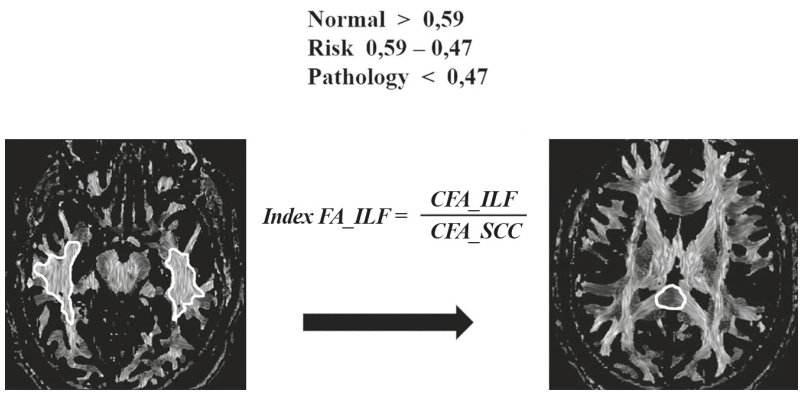

Fig. 12. Threshold values of CFA indexes for Inferior Longitudinalis Fasciculus (ILF) as neuroimaging markers of cognitive impairment risk

venient for operator). And, what is most important — it can be applied to evaluate status of certain patient, without collecting groups of control or using some "reference" CFA values for each region of interest. But for receiving indices some "stable" region is needed. In a number of investigations [39] splenium of corpus callosum (SCC) was determined as a region of least variable anisotropy, not depending upon vascular pathology and other age-related changes (Fig. 10).

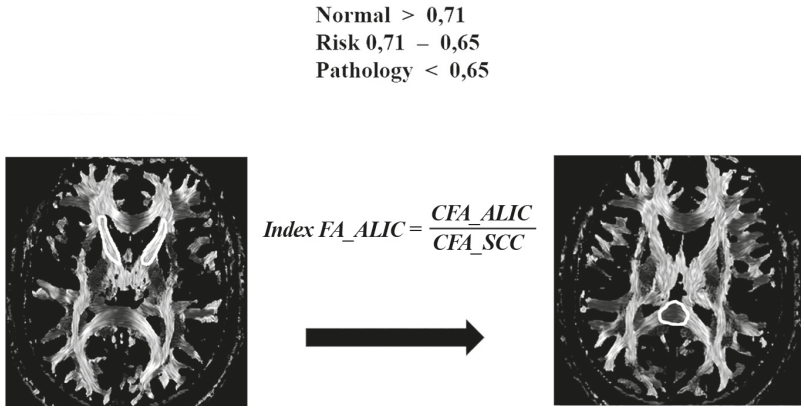

Fig. 13. Threshold values of CFA indexes for Anterior Limb of the Internal Capsule (ALIC) as neuroimaging markers of cognitive impairment risk

CFA indices are obtained by calculating ratio of CFA value in certain tract to the CFA value in splenium of corpus callosum for the same patient (Fig. 11, Fig. 12, Fig. 13). The boarders of risk intervals of cognitive decline in regions of interest (CFA indices) showing in the table below.

Table. **Cognitive decline risk in CFA indices**

Regions of interest	No risk of cognitive disorder	Initial risk of cognitive disorder	High risk of cognitive disorder (or there is already a disease)
Anterior Corona Radiata (ACR)	> 0.44	0.44–0.34	< 0.34
Inferior Longitudinal Fasciculus (ILF)	> 0.59	0.59–0.47	< 0.47
Anterior Limb of the Internal Capsule (ALIC)	> 0.71	0.71–0.65	< 0.65

Entering into initial risk interval of cognitive decline tells that it is necessary to take appropriate measures to prevent disease. At this stage patient must be additionally examined, including neuropsychological tests, and it is necessary to assign appropriate care recommendations and life style changing, intellectual exercises and memory training to increase cognitive reserve, preventing progress of accompanying pathology, influencing cerebral blood supply. Going out through the lower threshold values boarder of the CFA index in one or in all three zone may signal about severity of already presented cognitive disorder, that also require correction of the therapy [39].

Cerebral tracts' microstructural changes may also be detected using DT-MRI even before patients' claims on cognitive function decline. CFA indices and its absolute values changes can be indicators of latent pathological changes of nerve cells axons, taking place at initial stage of demyelinization, caused by vascular pathology. Application of

such vascular dementia neuroimaging markers provides an opportunity to have cognitive disorders prognosis and to make timely decisions on patient therapy and care [40].

Conclusions

Modern methods of structural visualization successfully supplement each other and may provide early detection of dementia, assisting to refine and to broaden our beliefs concerning pathophysiological processes, uderlaying cognitive dysfunction formation. Microstructural changes in cerebral pathways may also be detected using DTI before patients' active claims on cognitive function decline. This is important stage of diagnostic assistance for successful therapy of this disease for aged patients, as well as for its prevention for people of young and middle age.

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